Case Study 2
Brineura (cerliponase alfa): Real-World Challenges with an External Control Group

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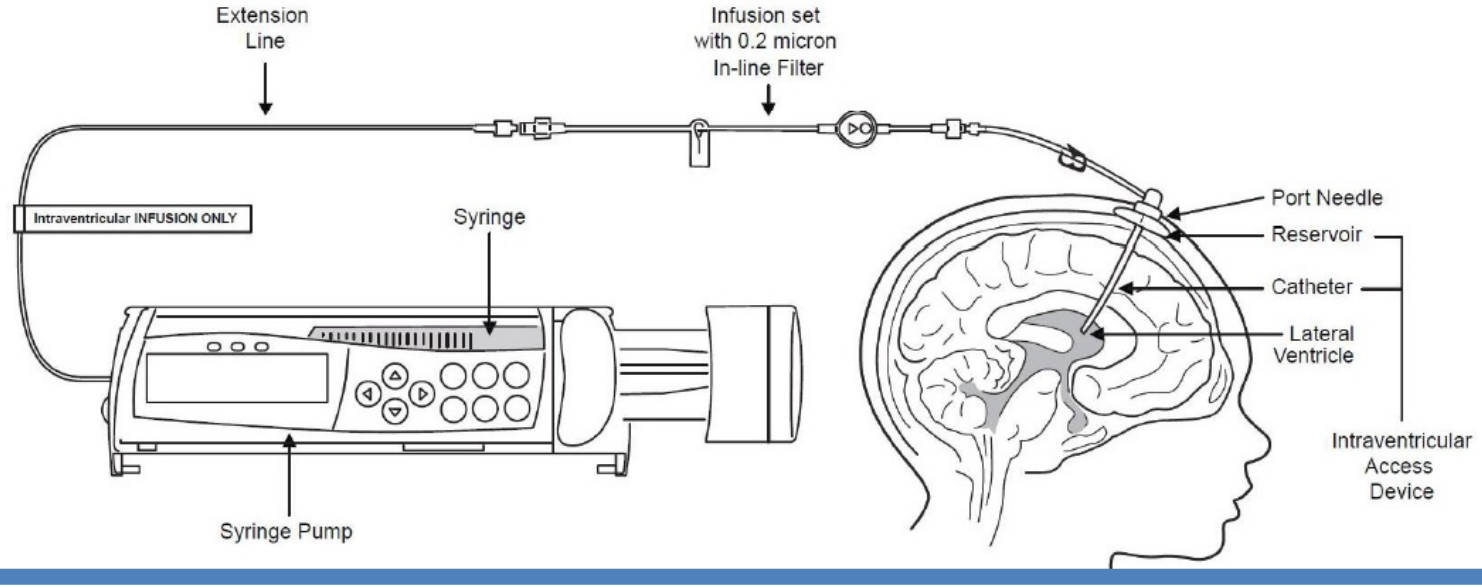
Disclosures

- No conflict of interests
- Nothing to disclose
- The views expressed in this presentation are those of the speaker and do not necessarily represent an official FDA position

Brinerua (Cerliponase Alfa)

- Approved in April 2017
  - **To slow the loss of ambulation in symptomatic pediatric patients 3 years of age and older with late infantile CLN2**
- Enzyme Replacement Therapy
  - Recombinant human tripeptidyl peptidase-1 (rhTPP1)
- Administered through an Intraventricular Device



CLN2 Disease
(Neuronal Ceroid Lipofuscinosis Type 2)

- Lysosomal storage disease due to TPP1 deficiency
- US incidence estimated 0.1-1/100,000 births/year

- Progressive neurodegenerative disease
- Classic Late Infantile NCL (cLINCL)
  - Symptom onset typically 2-4 years of age
  - Seizures, ataxia, language delay, developmental decline
  - Blindness, dementia, vegetative state
  - Death 8-15 yo

- At time of BLA submission, no approved therapy

Clinical Studies for Brineura Approval

- Pivotal Trial: single-arm, multi-national, open-label, 48 week study with long-term efficacy extension study
- Natural History Registry: European Registry of NCL
  - No pre-specified protocol, no required clinical data

	Efficacy Assessment	Methodology of Assessment	Frequency of Assessment
Treatment Trial (n=24)	Adapted CLN2 Motor & Language Scale	• Prospective Observation	Every 8 weeks
Natural History Registry (n=42)	Original Hamburg CLN2 Motor & Language Scale	• Prospective Observation • Retrospective Medical History • Retrospective Parental Interview	Not specified

Review Challenges due to Use of a Non-Concurrent External Control

- Comparability of Efficacy Assessments
  - Changes to the CLN2 Rating Scale itself
  - Different methodology of assessments
  - Different intervals for assessments
- Comparability of Populations

Primary Efficacy Endpoint: CLN2 Language Rating Scales

External Control		Single-Arm Treatment Study	
Language			
3	Normal	**3**	Apparently normal language. Intelligible and grossly age-appropriate. No decline noted yet.
2	Has become recognizable abnormal	**2**	Language has become recognizably abnormal: some intelligible words, may form short sentences to convey concepts, requests, or needs. This score signifies a decline from a previous level of ability (from the individual maximum reached by the child).
1	Hardly understandable	**1**	Hardly understandable. Few intelligible words.
0	Unintelligible or no language	**0**	No intelligible words or vocalizations.

From the Rater's Assessment Guide

Primary Efficacy Endpoint: CLN2 Motor Rating Scales

External Control		Single-Arm Treatment Study	
Motor			
3	Walks normally	**3**	Grossly normal gait. No prominent ataxia, no pathologic falls.
2	**Frequent falls**, clumsiness obvious	**2**	Independent gait, as defined by the ability to walk without support for ***10 steps***. Will have obvious instability, and may have **intermittent falls**.
1	No unaided walking or crawling only	**1**	Requires external assistance to walk, or can crawl only.
0	Immobile, mostly bedridden	**0**	Can no longer walk or crawl.

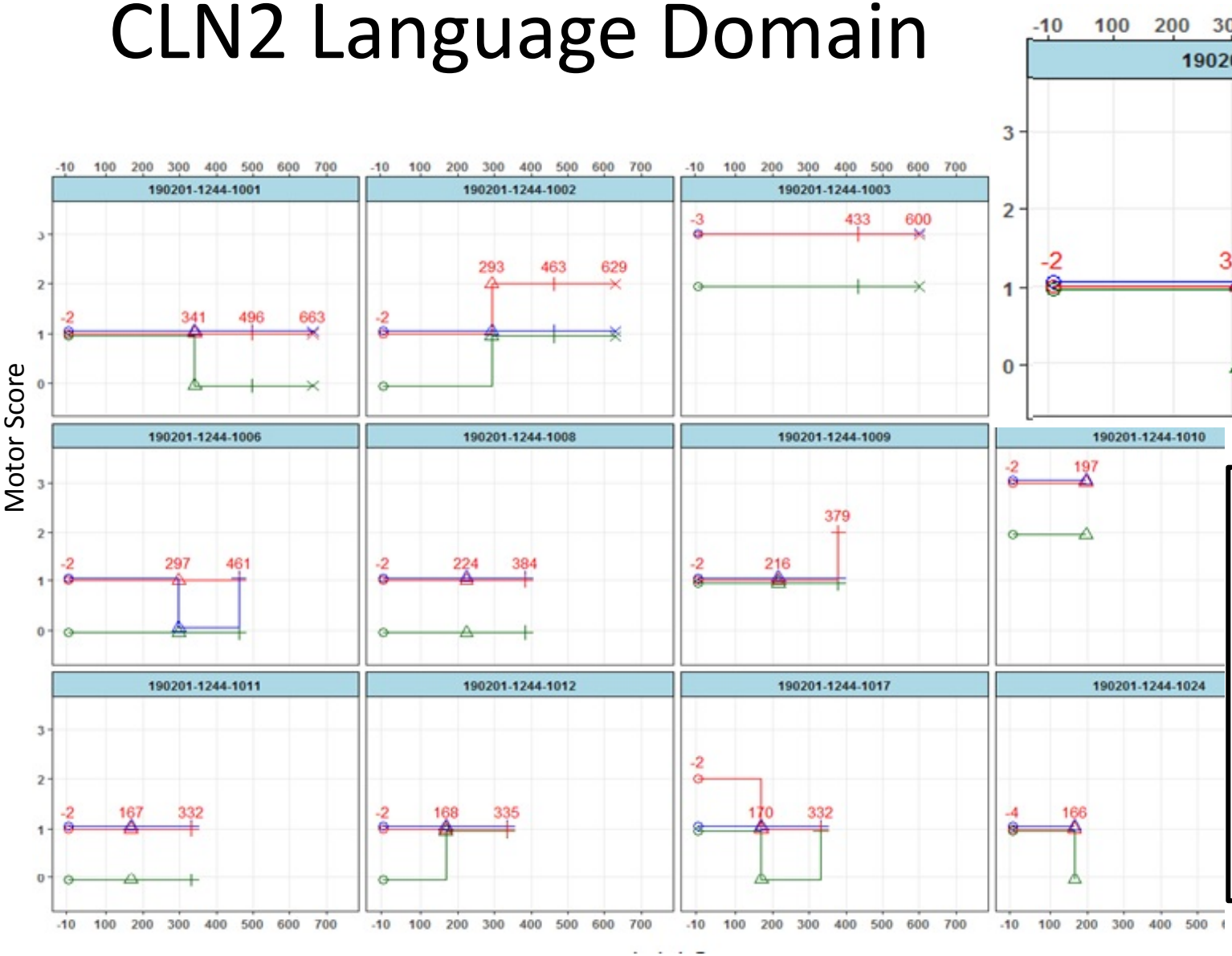
From the Rater's Assessment Guide

Scale Comparability Study

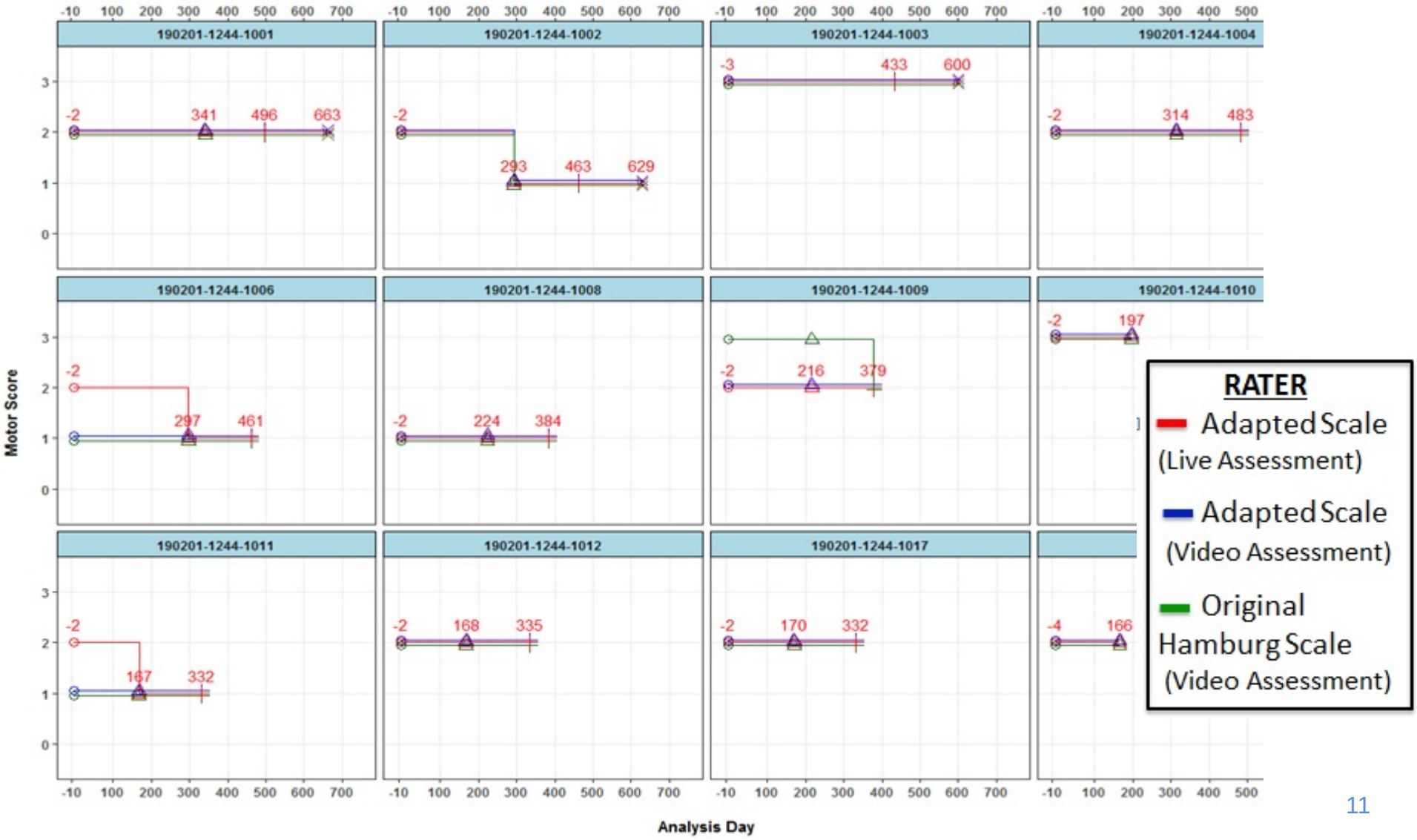
- **<u>Preferred Method:</u> Rescore Natural History Assessments from videos by assessors who rated subjects in the pivotal trial**
  - Not feasible

- **<u>Actual Method:</u> Video Assessment of CLN2 Rating Scale during Pivotal Trial by developers of both versions of the rating scale**
  - 36 videos from 12 subjects at 1 study site rated by 3 raters
    - Pivotal trial clinician ('live' assessment)
    - Trainer of pivotal trial clinician (video assessment)
    - Natural history CLN2 scale developer (video assessment)
  - Graphical evaluation of rater agreement & discordance

Comparability Study
CLN2 Language Domain



Comparability Study CLN2 Motor Domain



Assessment Frequency

- Natural History Study:

  - ≥ 2 CLN2 assessments (not 0 or 6) after 36 months
  - At least 6 months between 2 assessments

- Treatment Study:

  - Assessments every 8 weeks

- Overcame this limitation with conservative statistical assumptions
  - Last Observation Carried Forward (LOCF)

Treatment vs Natural History Demographic Data

	Controls (n=42)	Treatment Efficacy Population (n=22)
Sex		
Male	25 (**60%**)	7 (**32%**)
Female	17 (**40%**)	15 (**68%**)
Genotype		
2 common alleles	24 (**57%**)	9 (**41%**)
1 common alleles	11 (26%)	6 (27%)
No common allele	7 (**17%**)	7 (**32%**)
Decade Born		
Pre- 1980	4 (**10%**)	**0**
1980s	2 (**5%**)	**0**
1990s	19 (**45%**)	**0**
2000s	16 (**38%**)	12 (**55%**)
After 2010	1 (**2%**)	10 (**45%**)

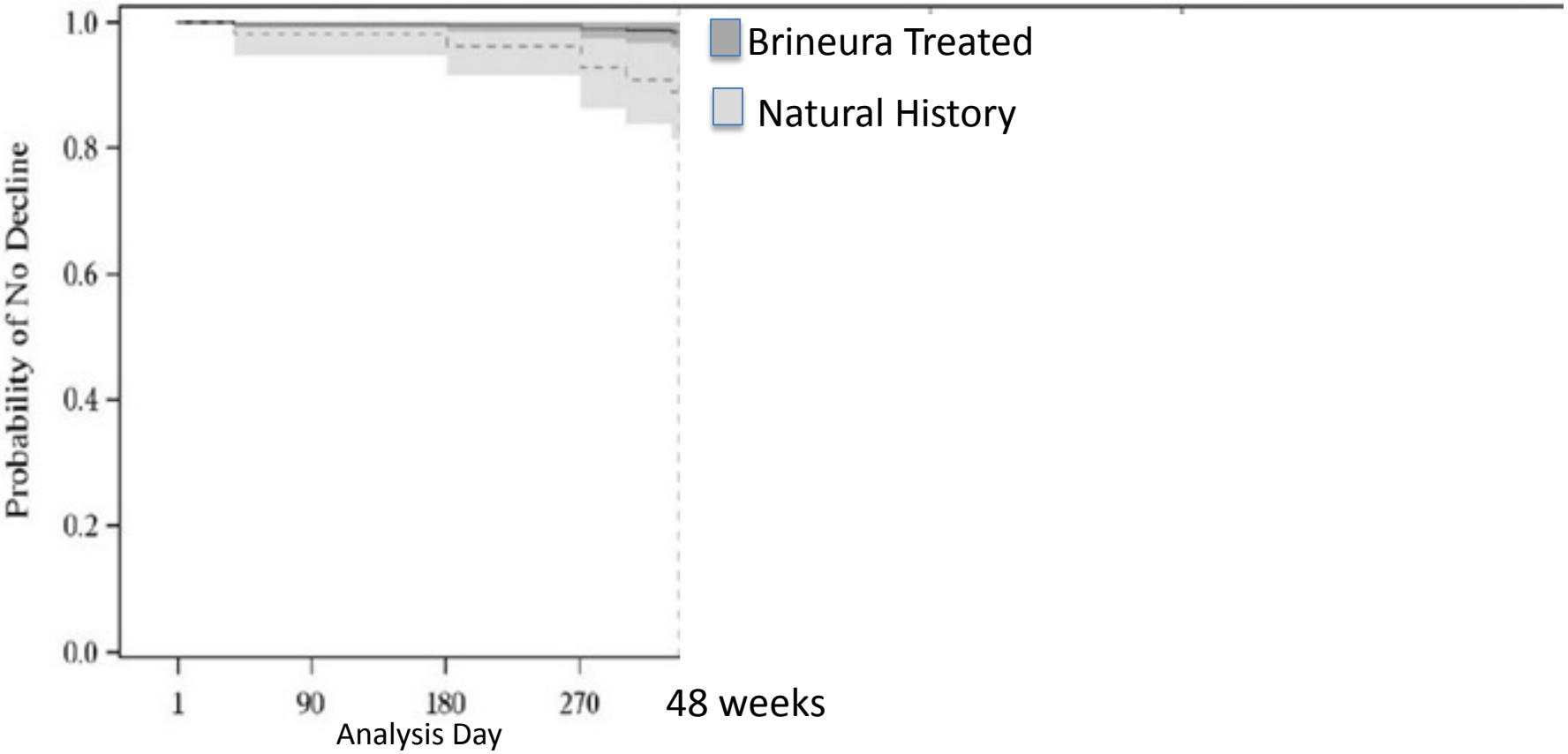
Analytical Methods

- Analyzed only CLN2 motor scores
- Primary analysis was a responder analysis
  - Sustained 2 category decline or score of 0
- Conservative statistical assumptions for natural history controls
- Potential confounders included in covariate & sensitivity analyses

- Study Duration
  - Efficacy data based on data-cut at 96 weeks (instead of 48 in initial BLA submission)

Efficacy

Cox Proportional Hazard Model Adjusting for Covariates Estimated Time to Unreversed 2-Category Decline or Unreversed Score of Zero in Motor Domain for Symptomatic Patients



Brineura Subjects at Risk

22 21

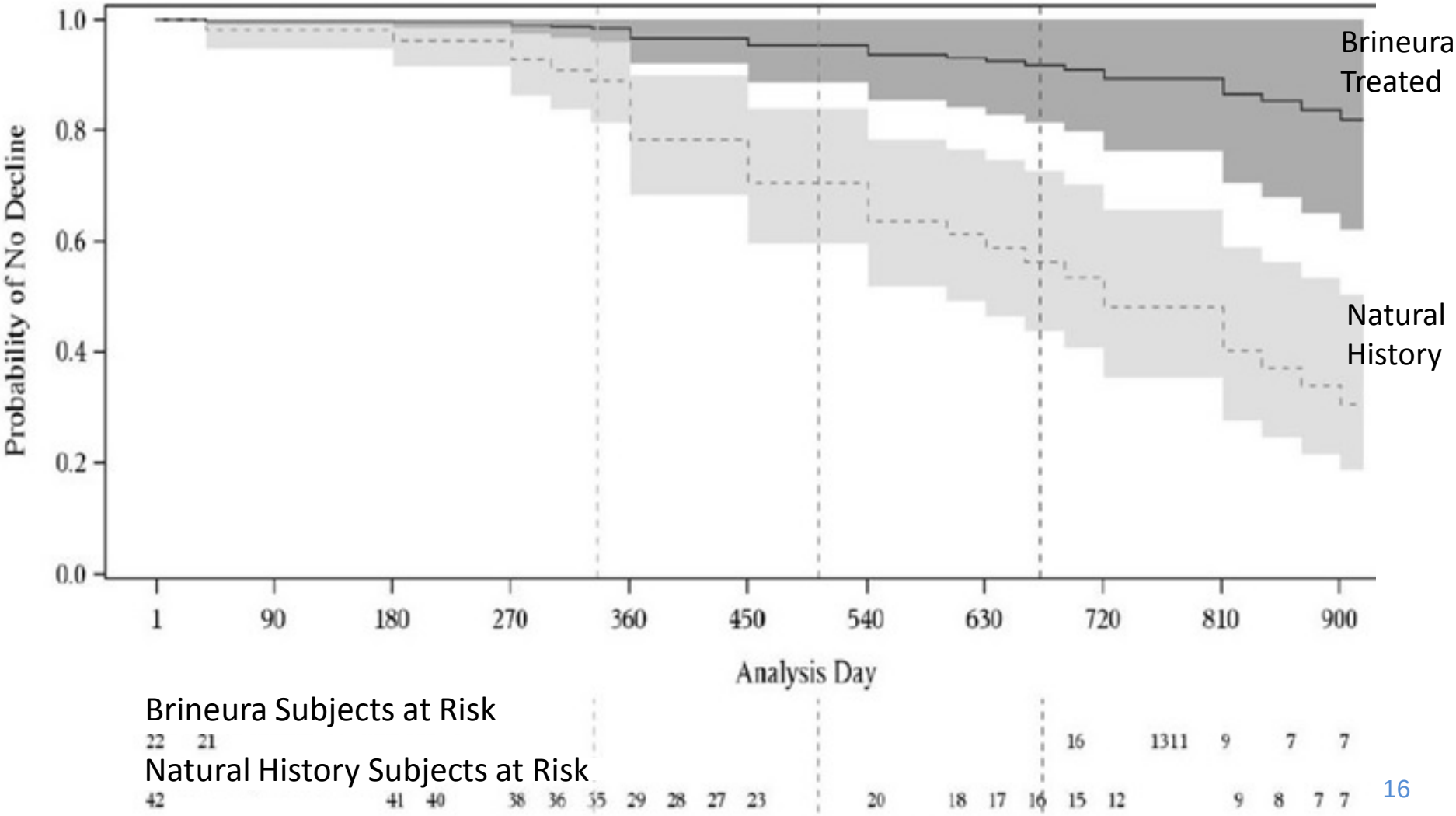
Natural History Subjects at Risk at Risk

42 41 40

Efficacy

Cox Proportional Hazard Model Adjusting for Covariates

Estimated Time to Unreversed 2-Category Decline or Unreversed Score of Zero in Motor Domain for Symptomatic Patients



Opportunities & Considerations

External Control Groups

- Assessment procedures should be optimized to obtain analyzable data
  - Standardization of instrument, rater training, instructions, & assessment intervals both within the control group and between control and treatment groups
- Ensuring population comparability between control and treatment groups enhances data interpretability
- Study duration should be sufficient to demonstrate impact on clinically meaningful endpoints
- Knowledge from well designed and conducted natural history studies can inform many aspects of clinical trials
  - Eligibility criteria, endpoint selection, study duration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